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 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
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 NEWS  9  Jun 03  New e-mail delivery for search results now available
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 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
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 NEWS 24  Sep 16  Experimental properties added to the REGISTRY file
 NEWS 25  Sep 16  Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 26  Sep 16  CA Section Thesaurus available in CAPLUS and CA
 NEWS 27  Oct 01  CASREACT Enriched with Reactions from 1907 to 1985

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               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> file ca,biosis, medline
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
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FILE 'MEDLINE' ENTERED AT 15:35:01 ON 11 OCT 2002

=> s diabetic cardiomyopathy?
L1 1065 DIABETIC CARDIOMYOPATHY?

=> s GLP-1?
TERM '1?' EXCEEDED TRUNCATION LIMITS - SEARCH ENDED
<------User Break------>
u
SEARCH ENDED BY USER
You have entered a truncated stem which occurs in too many terms.
Make the stem longer and try again. For example, if your original
term was 'degr?' to search for variations and the abbreviation for
'degradation', you could replace it with the expression '(degrdn OR
degrad?)'. If your search term was numeric, e.g., 'C>5', reduce the
size of the range.

=> s GLP-1
L2 3549 GLP-1

=> d his

(FILE 'HOME' ENTERED AT 15:34:48 ON 11 OCT 2002)

FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 15:35:01 ON 11 OCT 2002
L1 1065 S DIABETIC CARDIOMYOPATHY?
L2 3549 S GLP-1

=> s l1 and l2
L3 1 L1 AND L2

=> d

L3 ANSWER 1 OF 1 CA COPYRIGHT 2002 ACS
AN 136:350560 CA
TI Treatment of hibernating myocardium and **diabetic cardiomyopathy** with a **GLP-1** peptide
IN Ehlers, Mario
PA Coolidge, Thomas R., USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

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PI   WO 2002034285     A2   20020502       WO 2001-US32559  20011022
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
            PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
            US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2002146405     A1   20021010       US 2001-982978   20011022
PRAI US 2000-241834P   P    20001020
     US 2000-242139P   P    20001023
     US 2000-245234P   P    20001103


=> d ab,bib

L3   ANSWER 1 OF 1  CA  COPYRIGHT 2002 ACS
AB   Hibernating myocardium is characterized by viable myocardium with impaired
     function due to localized reduced perfusion.  Hibernating myocytes retain
     cellular integrity, but cannot sustain high-energy requirements of
     contraction.  High plasma levels of catecholamines, such as
     norepinephrine, are believed to be predictive of mortality from
     hibernating myocardium.  Likewise, high levels of catecholamines lead to
     cardiomyopathy in patients with diabetes.  GLP-1
     reduces plasma norepinephrine levels, and it thus is useful in a method of
     treating hibernating myocardium or diabetic
     cardiomyopathy.
AN   136:350560  CA
TI   Treatment of hibernating myocardium and diabetic
     cardiomyopathy with a GLP-1 peptide
IN   Ehlers, Mario
PA   Coolidge, Thomas R., USA
SO   PCT Int. Appl., 26 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------  ----  --------       ---------------  --------
PI   WO 2002034285     A2   20020502       WO 2001-US32559  20011022
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
            PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
            US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2002146405     A1   20021010       US 2001-982978   20011022
PRAI US 2000-241834P   P    20001020
     US 2000-242139P   P    20001023
     US 2000-245234P   P    20001103
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L6: Entry 5 of 6 File: USPT Aug 21, 2001

DOCUMENT-IDENTIFIER: US 6277819 B1
TITLE: Use of GLP-1 or analogs in treatment of myocardial infarction

Abstract Text (1):
This invention provides a method of reducing mortality and morbidity after myocardial infarction. GLP-1, a GLP-1 analog, or a GLP-1 derivative, is administered at a dose effective to normalize blood glucose.

Brief Summary Text (6):
Factors responsible for the poor prognosis among diabetic patients with acute myocardial infarction may act before, during, or after the acute event. They include diffuse coronary atheromatosis, with more advanced and widespread coronary artery disease, which, together with a possible diabetic cardiomyopathy, may contribute to a high prevalence of congestive heart failure. Autonomic neuropathy with impaired pain perception and increased resting heart rate variability may also be of importance. A coronary thrombus is an essential part of an evolving infarction, and notably, platelet activity, coagulation, and fibrinolytic functions have been found to be disturbed in diabetic patients [Davi G., et al., New England. J. Med., 322:1769-1774 (1990)].

Brief Summary Text (11):
The incretin hormone, glucagon-like peptide 1, abbreviated as GLP-1, is processed from proglucagon in the gut and enhances nutrient-induced insulin release [Krcymann B., et al., Lancet 2:1300-1303 (1987)]. Various truncated forms of GLP-1, are known to stimulate insulin secretion (insulinotropic action) and cAMP formation [see, e g., Mojsov, S., Int. J. Peptide Protein Research, 40:333-343 (1992)]. A relationship between various in vitro laboratory experiments and mammalian, especially human, insulinotropic responses to exogenous administration of GLP-1, GLP-1(7-36) amide, and GLP-1(7-37) acid has been established [see, e.g., Nauck, M. A., et al., Diabetologia, 36:741-744 (1993); Gutniak, M., et al., New England J. of Medicine, 326(20):1316-1322 (1992); Nauck, M. A., et al., J. Clin. Invest., 91:301-307 (1993); and Thorens, B., et al., Diabetes, 42:1219-1225 (1993)]. GLP-1(7-36) amide exerts a pronounced antidiabetogenic effect in insulin-dependent diabetics by stimulating insulin sensitivity and by enhancing glucose-induced insulin release at physiological concentrations [Gutniak M., et al., New England J. Med. 326:1316-1322 (1992)]. When administered to non-insulin dependent diabetics, GLP-1(7-36) amide stimulates insulin release, lowers glucagon secretion, inhibits gastric emptying and enhances glucose utilization [Nauck, 1993; Gutniak, 1992; Nauck, 1993].

Brief Summary Text (12):
The use of GLP-1 type molecules for prolonged therapy of diabetes has been obstructed because the serum half-life of such peptides is quite short. For example, GLP-1(7-37) has a serum half-life of only 3 to 5 minutes. GLP-1(7-36) amide has a half-life of about 50 minutes when administered subcutaneously. Thus, these GLP molecules must be administered as a continuous infusion to achieve a prolonged effect [Gutniak M., et al., Diabetes Care 17:1039-1044 (1994)]. In the present invention, GLP-1's short half-life and the consequent need for continuous administration are not disadvantages because the patient is typically bed-ridden, in a cardiac intensive care unit, where fluids are continuously administered parenterally.

Brief Summary Text (14):
The present invention provides a method of reducing mortality and morbidity after

myocardial infarction, comprising administering a compound from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives, and pharmaceutically-acceptable salts thereof, at a dose effective to normalize blood glucose, to a patient in need thereof.

Drawing Description Text (2):
FIG. 1 is a graph showing the effect of continuous infusion GLP-1 (7-36) amide on average blood glucose concentration (mM) {character pullout} in five NIDDM patients during the night. The graph also depicts the effect of continuous insulin infusion on average blood glucose concentration {character pullout} in the same five NIDDM patients, but on a different night.

Drawing Description Text (3):
FIG. 2 is a graph showing the effect of GLP-1 (7-36) amide infusion on average blood glucose concentration (mM) {character pullout} in five NIDDM patients when infused during the day, for three hours starting at the beginning of each of three meals. The graph also depicts the effect of subcutaneous injection of insulin on average blood glucose concentration {character pullout} in the same five NIDDM patients, but on a different day, and with injection shortly before each meal.

Detailed Description Text (2):
"GLP-1" means GLP-1(7-37). By custom in the art, the amino-terminus of GLP-1(7-37) has been assigned number 7 and the carboxy-terminus, number 37. The amino acid sequence of GLP-1(7-37) is well-known in the art, but is presented below for the reader's convenience:

Detailed Description Text (3):
A "GLP-1 analog" is defined as a molecule having one or more amino acid substitutions, deletions, inversions, or additions compared with GLP-1. GLP-1 analogs known in the art include, for example, GLP-1(7-34) and GLP-1(7-35), GLP-1(7-36), Gln.sup.9 -GLP-1(7-37), D-Gln.sup.9 -GLP-1(7-37), Thr.sup.16 -Lys.sup.18 -GLP-1(7-37), and Lys.sup.18 -GLP-1(7-37). Preferred GLP-1 analogs are GLP-1(7-34) and GLP-1(7-35), which are disclosed in U.S. Pat. No: 5,118,666, herein incorporated by reference, and also GLP-1(7-36), which are the biologically processed forms of GLP-1 having insulinotropic properties. Other GLP-1 analogs are disclosed in U.S. Pat. No. 5,545,618 which is incorporated herein by reference.

Detailed Description Text (4):
A "GLP-1 derivative" is defined as a molecule having the amino acid sequence of GLP-1 or of a GLP-1 analog, but additionally having chemical modification of one or more of its amino acid side groups, .alpha.-carbon atoms, terminal amino group, or terminal carboxylic acid group. A chemical modification includes, but is not limited to, adding chemical moieties, creating new bonds, and removing chemical moieties. Modifications at amino acid side groups include, without limitation, acylation of lysine .epsilon.-amino groups, N-alkylation of arginine, histidine, or lysine, alkylation of glutamic or aspartic carboxylic acid groups, and deamidation of glutamine or asparagine. Modifications of the terminal amino include, without limitation, the des-amino, N-lower alkyl, N-di-lower alkyl, and N-acyl modifications. Modifications of the terminal carboxy group include, without limitation, the amide, lower alkyl amide, dialkyl amide, and lower alkyl ester modifications. Lower alkyl is C.sub.1 -C.sub.4 alkyl. Furthermore, one or more side groups, or terminal groups, may be protected by protective groups known to the ordinarily-skilled protein chemist. The .alpha.-carbon of an amino acid may be mono- or SEQ ID NO: 6 dimethylated.

Detailed Description Text (5):
A preferred group of GLP-1 analogs and derivatives for use in the present invention is composed of molecules of the formula:

Detailed Description Text (7):
Numerous GLP-1 analogs and derivatives having an isoelectric point in this range have been disclosed and include, for example:

Detailed Description Text (8):
Another preferred group of active compounds for use in the present invention is disclosed in WO 91/11457, and consists essentially of GLP-1(7-34), GLP-1(7-35),

GLP-1(7-36), or GLP-1(7-37), or the amide form thereof, and pharmaceutically-acceptable salts thereof, having at least one modification selected from the group consisting of:

Detailed Description Text (14):
Because the enzyme, dipeptidyl-peptidase IV (DPP IV), may be responsible for the observed rapid in vivo inactivation of administered GLP-1, [see, e.g., Mentlein, R., et al., Eur. J. Biochem., 214:829-835 (1993)], administration of GLP-1 analogs and derivatives that are protected from the activity of DPP IV is preferred, and the administration of Gly.sup.8 -GLP-1(7-36)NH.sub.2, Val.sup.8 -GLP-1(7-37)OH, a-methyl-Ala.sup.8 -GLP-1(7-36)NH.sub.2, and Gly.sup.8 -Gln.sup.21 -GLP-1(7-37)OH, or pharmaceutically-acceptable salts thereof, is more preferred.

Detailed Description Text (25):
The use of GLP-1(7-36) amide, or a pharmaceutically-acceptable salt thereof, in the present invention is most highly preferred. The amino acid sequence of GLP-1(7-36) amide is:

Detailed Description Text (26):
Methods for preparing the active compound used in the present invention, namely, GLP-1, an GLP-1 analog, or a GLP-1 derivative used in the present invention are well-known, and are described in U.S. Pat. Nos. 5,118,666, 5,120,712, and 5,523,549, which are incorporated by reference.

Detailed Description Text (38):
a) isolating a natural DNA sequence encoding a GLP-1 molecule or constructing a synthetic or semi-synthetic DNA coding sequence for a GLP-1 molecule,

Detailed Description Text (41):
d) culturing the transformed host cell under conditions that will permit expression of a GLP-1 molecule, and

Detailed Description Text (42):
e) recovering and purifying the recombinantly produced GLP-1 molecule.

Detailed Description Text (44):
Synthetic genes, the in vitro or in vivo transcription and translation of which results in the production of a GLP-1 molecule, may be constructed by techniques well known in the art. Owing to the natural degeneracy of the genetic code, the skilled artisan will recognize that a sizable yet definite number of DNA sequences may be constructed, all of which encode GLP-1 molecules.

Detailed Description Text (46):
To express the amino acid portion of a compound used in the present invention, one inserts the engineered synthetic DNA sequence in any one of many appropriate recombinant DNA expression vectors through the use of appropriate restriction endonucleases. See generally Maniatis et al. (1989) Molecular Cloning; A Laboratory Manual, Cold Springs Harbor Laboratory Press, N.Y., Vol. 1-3. Restriction endonuclease cleavage sites are engineered into either end of the GLP-1 molecule-encoding DNA to facilitate isolation from, and integration into, amplification and expression vectors well-known in the art. The particular endonucleases employed will be dictated by the restriction endonuclease cleavage pattern of the parent expression vector employed. Restriction sites are chosen to properly orient the coding sequence with control sequences, thereby achieving proper in-frame reading and expression of the protein of interest. The coding sequence must be positioned to be in proper reading frame with the promoter and ribosome binding site of the expression vector, both of which are functional in the host cell in which the protein is to be expressed.

Detailed Description Text (58):
Alterations to a precursor GLP-1 or GLP-1 analog amino acid sequence, to produce a desired GLP-1 analog or GLP-1 derivative, are made by well-known methods: chemical modification, enzymatic modification, or a combination of chemical and enzymatic modification of GLP-1 precursors. The techniques of classical solution phase methods and semi-synthetic methods may also be useful for preparing the GLP-1 molecules used in the present invention. Methods for preparing the GLP-1 molecules of the present

invention are well known to an ordinarily skilled peptide chemist.

Detailed Description Text (60):
For example, an N-hydroxy-succinimide ester of octanoic acid can be added to the lysyl-epsilon amine using 50% acetonitrile in borate buffer. The peptide can be acylated either before or after the imidazolic group is added. Moreover, if the peptide is prepared recombinantly, acylation prior to enzymatic cleavage is possible. Also, the lysine in the GLP-1 derivative can be acylated as taught in W096-29342, which is incorporated herein by reference.

Detailed Description Text (61):
The existence and preparation of a multitude of protected, unprotected, and partially-protected, natural and unnatural, functional analogs and derivatives of GLP-1 (7-36)amide and GLP-1 (7-37) molecules have been described in the art [see, e.g., U.S. Pat. No. 5,120,712 and 5,118,666, which are herein incorporated by reference, and Orskov, C., et al., J. Biol. Chem., 264(22):12826-12829 (1989) and WO 91/11457 (Buckley, D. I., et al., published Aug. 8, 1991)].

Detailed Description Text (62):
Optionally, the amino and carboxy terminal amino acid residues of GLP-1 derivatives may be protected, or, optionally, only one of the termini is protected. Reactions for the formation and removal of such protecting groups are described in standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York (1973); Green, T. H., "Protective Groups in Organic Synthesis", Wiley, New York (1981); and "The Peptides", Vol. I, Schroder and Lubke, Academic Press London and New York (1965). Representative amino-protecting groups include, for example, formyl, acetyl, isopropyl, butoxycarbonyl, fluorenylmethoxycarbonyl, carbobenzyloxy, and the like. Representative carboxy-protecting groups include, for example, benzyl ester, methyl ester, ethyl ester, t-butyl ester, p-nitro phenyl ester, and the like.

Detailed Description Text (63):
Carboxy-terminal, lower-alkyl-ester, GLP-1 derivatives used in the present invention are prepared by reacting the desired (C.sub.1 -C.sub.4) alkanol with the desired polypeptide in the presence of a catalytic acid such as hydrochloric acid. Appropriate conditions for such alkyl ester formation include a reaction temperature of about 50.degree. C. and reaction time of about 1 hour to about 3 hours. Similarly, alkyl ester derivatives of the Asp and/or Glu residues can be formed.

Detailed Description Text (65):
A pharmaceutically-acceptable salt form of GLP-1, of a GLP-1 analog, or of a GLP-1 derivative may be used in the present invention. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and, especially, hydrochloric acid.

Detailed Description Text (67):
A GLP-1, GLP-1 analog, or GLP-1 derivative used in the present invention may be formulated with one or more excipients before use in the present invention. For example, the active compound used in the present invention may be complexed with a divalent metal cation by well-known methods. Such metal cations include, for example, Zn.sup.++, Mn.sup.++, Fe.sup.++, Co.sup.++, Cd.sup.++, Ni.sup.++, and the like.

Detailed Description Text (79):
The dose of GLP-1, GLP-1 analog, or GLP-1 derivative effective to normalize a patient's blood glucose level will depend on a number of factors, among which are included, without limitation, the patient's sex, weight and age, the severity of inability to regulate blood glucose, the underlying causes of inability to regulate blood glucose, whether glucose, or another carbohydrate source, is simultaneously administered, the route of administration and bioavailability, the persistence in the body, the formulation, and the potency. Where administration is continuous, a suitable dosage rate is between 0.25 and 6 pmol/kg body weight/min, preferably from about 0.5 to about 1.2 pmol/kg/min. Where administration is intermittent, the dose per administration should take into account the interval between doses, the bioavailability of GLP-1, GLP-1 analog, or GLP-1 derivative, and the level needed to effect normal blood glucose. It is within the skill of the ordinary physician to titrate the dose and rate of administration of GLP-1, GLP-1 analog, or GLP-1 derivative to achieve the desired clinical result.

Detailed Description Text (82):
GLP-1 (7-36) amide was administered by a subcutaneous infusion at a dose rate of 1.2 pmol/kg/hr, for ten hours during the night, to five patients having non-insulin dependent diabetes (NIDDM). As a control, insulin was continuously infused in the same five patients, but on a different day than the GLP-1 (7-36) amide infusion. The rate of insulin infusion was adjusted every two hours to achieve optimum control, and to avoid hypoglycemia. As demonstrated by the data in Table 1, and in FIG. 1, subcutaneous infusion of GLP-1 (7-36) amide nearly normalized blood glucose without inducing hypoglycemia in any of the patients. The metabolic control with GLP-1 (7-36) amide was better than that achieved by insulin, and the average blood glucose level was lower for GLP-1 (7-36) amide treatment than for the control by a statistically significant amount at 23:00, 0:00, and at 1:00.

Detailed Description Text (84):
During the day, GLP-1 (7-36) amide was infused into five NIDDM patients for three hours during breakfast, lunch, and dinner. The infusion times were 7:30-10:30 (breakfast), 10:30-1:30 (lunch), and 4:30-7:30 (dinner), as indicated in FIG. 2. In a control experiment in the same five NIDDM patients conducted on a different day, insulin was injected subcutaneously just before the start of the meals, as indicated in FIG. 2. While GLP-1 was infused, the post-prandial glucose excursions observed with insulin injection were eliminated; and normal blood glucose levels were maintained. Immediately after terminating each GLP-1 (7-36) amide infusion, the blood glucose level increased significantly. No untoward side effects of GLP-1 (7-36) amide were observed. These data indicate that GLP-1 (7-36) amide infusion more effectively controls post-prandial glucose levels than insulin injection, and that the control is effective as long as GLP-1 (7-36) amide infusion is continued.

Detailed Description Paragraph Table (3):
GLP-1 (7-36)NH.sub.2 Gly.sup.8 -GLP-1 (7-36)NH.sub.2 Gln.sup.9 -GLP-1 (7-37) D-Gln.sup.9 -GLP-1 (7-37) acetyl-Lys.sup.9 -GLP-1 (7-37) Thr.sup.9 -GLP-1 (7-37) D-Thr.sup.9 -GLP-1 (7-37) Asn.sup.9 -GLP-1 (7-37) D-Asn.sup.9 -GLP-1 (7-37) Ser.sup.22 -Arg.sup.23 -Arg.sup.24 -Gln.sup.26 -GLP-1 (7-37) SEQ ID NO:6 Thr.sup.16 -Lys.sup.18 -GLP-1 (7-37) Lys.sup.18 -GLP-1 (7-37) Arg.sup.23 -GLP-1 (7-37) Arg.sup.24 -GLP-1 (7-37), and the like [see, e.g., WO 91/11457].

Detailed Description Paragraph Table (8):
TABLE 1 Average blood glucose levels for five NIDDM patients continuously infused for ten hours during the night with GLP-1 (7-36) amide. In a control study with the same patients on a different day, insulin was administered by continuous infusion. Insulin Infusion GLP-1 Infusion (Control) Average Average Blood Blood Glucose Std. Error Glucose Std. Error Hour (mM) (mM) (mM) (mM) 21:00 7.5 0.45 6.9 0.68 22:00 5.4 0.76 6.6 0.55 23:00 4.1 0.16 5.9 0.98 0:00 4.4 0.23 5.6 0.90 1:00 4.4 0.29 5.1 0.58 2:00 4.8 0.34 5.2 0.58 3:00 5.2 0.41 5.4 0.30 4:00 5.4 0.41 5.7 0.25 5:00 5.8 0.41 6.0 0.30 6:00 6.0 0.45 6.1 0.38 7:00 6.2 0.45 6.1 0.33

Detailed Description Paragraph Table (9):
TABLE 2 Average blood glucose levels for five NIDDM patients infused with GLP-1 (7-36) amide for three hours, beginning at the start of each meal. In a control study with the same patients on a different day, insulin was administered by subcutaneous

injection just before each meal. Meals began at 7:30, 10:30, and at 4:30. Insulin Subcutaneous GLP-1 Infusion Injection Average Average Blood Blood Glucose Std. Error Glucose Std. Error Hour (mM) (mM) (mM) (mM) 7:00 5.4 0.35 6.1 0.41 8:00 4.9 0.38 7.0 0.51 9:00 5.7 0.59 9.1 0.74 10:00 5.8 1.06 9.9 0.78 11:00 8.1 0.94 8.2 0.76 12:00 9.4 0.59 6.5 0.74 13:00 7.2 1.18 9.1 0.90 14:00 5.3 1.21 8.1 0.91 15:00 7.2 0.71 7.0 0.87 16:00 10.4 0.26 7.2 0.57 17:00 9.2 1.06 6.5 0.59 18:00 5.7 1.59 7.3 0.65 19:00 6.6 0.94 6.1 0.59 20:00 8.3 0.71 6.0 0.41 21:00 9.3 0.71 6.4 0.44

CLAIMS:

1. A method of reducing mortality and morbidity after myocardial infraction, comprising administering to a patient in need thereof, a compound selected from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives and pharmaceutically-acceptable salts thereof, at a dose effective to normalize blood glucose.

13. A method of reducing mortality and morbidity after myocardial infraction, comprising administering a GLP-1 analog to a patient in need thereof at a dose effective to normalize blood glucose, said GLP-1 analog being represented by the following structural formula:

R.sub.1 --X--Glu--Gly--Thr--Phe--Thr--Ser--Asp--Val--Ser--Ser--Tyr--Leu--Y--Gly--Gln--Ala--Ala--Lys--Z--Phe--Ile--Ala--Trp--Leu--Val--Lys--Gly--Arg--R.sub.2

and pharmaceutically-acceptable salts thereof,

wherein:

R.sub.1 is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, .beta.-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Ala, Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gin, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

R.sub.2 is selected from the group consisting of NH.sub.2, and Gly--OH;

provided that the GLP-1 analog has an isoelectric point in the range from about 6.0 to about 9.0 and further providing that when R.sub.1 is His, X is Ala, Y is Glu, and Z is Glu, R.sub.2 must be NH.sub.2.

14. A method of reducing mortality and morbidity after myocardial infraction in a patient with non-insulin dependent diabetes, said method comprising the step of administering to the patient, at a dose effective to normalize blood glucose, a compound selected from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives and pharmaceutically-acceptable salts thereof.

15. A method of reducing mortality and morbidity after myocardial infraction in a patient with non-insulin dependent diabetes, said method comprising the step of administering to the patient, at a dose effective to normalize blood glucose, a GLP-1 analog represented by the following structural formula:

R.sub.1 --X--Glu--Gly--Thr--Phe--Thr--Ser--Asp--Val--Ser--Ser--Tyr--Leu--Y--Gly--Gln--Ala--Ala--Lys--Z--Phe--Ile--Ala--Trp--Leu--Val--Lys--Gly--Arg--R.sub.2

and pharmaceutically-acceptable salts thereof,

wherein:

R.sub.1 is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, .beta.-hydroxy-histidine, homohistidine,

· àlpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Ala, Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gin, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

R.sub.2 is selected from the group consisting of NH.sub.2, and Gly--OH;

provided that the GLP-1 analog has an isoelectric point in the range from about 6.0 to about 9.0 and further providing that when R.sub.1 is His, X is Ala, Y is Glu, and Z is Glu, R.sub.2 must be NH.sub.2.

16. A method of reducing mortality and morbidity after myocardial infraction in a patient having a blood glucose level greater than 11 mmole/liter, said method comprising the step of administering to the patient, at a dose effective to normalize blood glucose, a compound selected from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives and pharmaceutically-acceptable salts thereof.

17. A method of reducing mortality and morbidity after myocardial infraction in a patient having a blood glucose level greater than 11 mmole/liter, said method comprising the step of administering to the patient, at a dose effective to normalize blood glucose, a GLP-1 analog represented by the following structural formula:

R.sub.1 --X--Glu--Gly--Thr--Phe--Thr--Ser--Asp--Val--Ser--Ser--Tyr--Leu--Y--Gly--G
ln--Ala--Ala--Lys--Z--Phe--Ile--Ala--Trp--Leu--Val--Lys--Gly--Arg--R.sub.2

and pharmaceutically-acceptable salts thereof,

wherein:

R.sub.1 is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, .beta.-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Ala, Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

R.sub.2 is selected from the group consisting of NH.sub.2, and Gly--OH;

provided that the GLP-1 analog has an isoelectric point in the range from about 6.0 to about 9.0 and further providing that when R.sub.1 is His, X is Ala, Y is Glu, and Z is Glu, R.sub.2 must be NH.sub.2.

18. A method of reducing mortality and morbidity after myocardial infraction in a patient with abnormal glucose tolerance, said method comprising the step of administering to the patient, at a dose effective to normalize blood glucose, a compound selected from the group consisting of GLP-1, GLP-1 analogs, GLP-1 derivatives and pharmaceutically-acceptable salts thereof.

19. A method of reducing mortality and morbidity after myocardial infraction in a patient having abnormal glucose tolerance, said method comprising the step of a GLP-1 analog to the patient, at a dose effective to normalize blood glucose, a GLP-1 analog represented by the following structural formula:

R.sub.1 --X--Glu--Gly--Thr--Phe--Thr--Ser--Asp--Val--Ser--Ser--Tyr--Leu--Y--Gly--G
ln--Ala--Ala--Lys--Z--Phe--Ile--Ala--Trp--Leu--Val--Lys--Gly--Arg--R.sub.2

and pharmaceutically-acceptable salts thereof,

wherein:

R.sub.1 is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, .beta.-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Ala, Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

R.sub.2 is selected from the group consisting of NH.sub.2, and Gly--OH;

provided that the GLP-1 analog has an isoelectric point in the range from about 6.0 to about 9.0 and further providing that when R.sub.1 is His, X is Ala, Y is Glu, and Z is Glu, R.sub.2 must be NH.sub.2.

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